REMARKS

Claims 1-7 and 10-18 are currently under consideration in this application. New Claims 28-32 have been entered. Support for these claims is found throughout the specification, for example, at pages 20-25 (disclosing medical devices comprising a surface layer that can include osteopontin and/or a thrombospondin 2 antisense molecule).

In view of the foregoing claim amendments, and the arguments that follow, applicants respectfully submit that all of the pending claims are in condition for allowance. Reconsideration and favorable action is requested.

Objection to the Specification

The Examiner objected to the specification because of the presence of hyperlinks at page 7, lines 3-4 and 18. The aforementioned hyperlinks have been canceled from the specification. Consequently, the Examiner's objection is moot.

Rejection of Claims 1-7 and 10-18 Under 35 U.S.C. § 1.12, First Paragraph, for Alleged Lack of Written Description

The Examiner notes that the instant specification discloses the sequence of a thrombospondin 2 (TSP2) gene (SEQ ID NO:3), but asserts that disclosure of the TSP2 gene does not provide sufficient description that would allow one of skill in the art to use SEQ ID NO:3 to predict the structure of any/all antisense TSP2 nucleic acids.

Applicants first respond to the Examiner's rejection as applied to Claims 6 and 7. Claim 6 recites the use of an antisense thrombospondin 2 nucleic acid molecule that is at least 90% identical to the complement of a thrombospondin 2 cDNA consisting of the nucleic acid sequence set forth in SEQ ID NO:3. Applicants submit that the subject matter defined by Claim 6 is clearly described by its percentage of sequence identity to the complement of the

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TSP2 cDNA set forth in SEQ ID NO:3. Moreover, a method for determining the percentage of sequence identity is set forth at page 7, lines 1-9, of the specification.

With respect to Claim 7, the antisense thrombospondin nucleic acid molecules used in the practice of the claimed invention are described as hybridizing under stringent conditions to a thrombospondin 2 cDNA molecule consisting of the nucleic acid sequence set forth in SEQ ID NO:3. The term "hybridize under stringent conditions" is defined in the specification at page 6, lines 4-19. Moreover, applicants submit that characterization of the antisense thrombospondin 2 nucleic acid molecules with reference to their ability to hybridize to the nucleic acid sequence set forth in SEQ ID NO:3 is consistent with Example 9 of the Revised Interim Written Description Guidelines promulgated by the United States Patent and Trademark Office on March 7, 2000.

More generally, with respect to the Examiner's rejection of Claims 1-7 and 10-18, the Federal Circuit has recently clarified that "[i]t is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Thus, the written description requirement may be met by disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure. *Id.* (citing U.S.P.T.O. Written Description Guidelines, 66 Fed. Reg. at 1106). The characteristics of useful antisense TSP2 molecules are described at pages 17 and 18 of the present application. The functional characteristics of the antisense thrombospondin 2 nucleic acid molecules is that they interact with thrombospondin 2 messenger RNA to inhibit production of thrombospondin 2. With respect to the structure of the thrombospondin 2 antisense nucleic acid molecules, one of ordinary skill in the art would recognize that they are each complementary to a portion of a thrombospondin 2 gene. Applicants submit that it is routine optimization to determine which

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portions of a thrombospondin 2 gene are suitable targets for a thrombospondin 2 antisense nucleic acid molecule.

In view of the foregoing arguments, applicants submit that the invention defined by Claims 1-7 and 10-18 is fully described and supported by the specification.

Rejection of Claims 1-7 and 10-18 Under 35 U.S.C. § 1.12, First Paragraph, for Alleged Lack of Enablement

The Examiner argues that the specification does not provide particular guidance or particular direction for a method for modulating the amount or biological activity of thrombospondin 2 using a thrombospondin 2 antisense nucleic acid molecule. The Examiner acknowledges that Example 1 of the instant application discloses that wild type mice implanted with a device including a surface collagen layer including an antisense thrombospondin 2 construct displayed an increase in foreign body capsule blood vessel density. Applicants submit that Example 1 therefore discloses at least one method for effectively delivering antisense thrombospondin 2 nucleic acid molecules to a mammalian subject; by incorporating the antisense nucleic acid molecules into the surface layer of an implanted medical device, thereby improving vascularization of the foreign body that forms around the implanted device, and so extending the useful life of the implanted device.

The Examiner argues that the specification provides no particular nexus between the increase in foreign body capsule blood vessel density in mice, and modulating the amount, or biological activity, of thrombospondin 2 to improve the wound response in humans. Contrary to the Examiner's assertion, applicants submit that mouse is an art-recognized model for studying the mammalian wound response (and the formation of blood vessels associated with the wound response), and that results obtained in mice with respect to the wound response can be extrapolated to human beings. For example, submitted herewith as Attachment A is a copy of a

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publication that discloses that platelet derived growth factor (PDGF), in combination with transforming growth factor alpha (TGF-α) improve wound healing in genetically diabetic mice (R.L. Brown et al., *J. Surgical Research 56*:562-570 (1994)). Submitted herewith as Attachment B is a copy of a publication that discloses that recombinant PDGF is now an accepted drug for promoting wound healing in diabetic foot ulcers (M.K. Nagai and J.M. Embil, *Expert Opin. Biol. Ther. 2*(2):211-218 (2002)). Additionally, submitted herewith as Attachment C is a copy of a publication that discloses the results of human clinical trials evaluating the safety and efficacy of recombinant PDGF (sold under the trade name becaplermin) for treating diabetic ulcers (J.M. Smiell et al., *Wound Repair and Regeneration 7*:335-346 (1999)).

Additionally, submitted herewith as Attachment D is a copy of a publication that discloses genetically modified mice having a cardiac myocyte-specific deletion of the vascular endothelial growth factor gene. The hearts of these transgenic mice had fewer coronary microvessels than normal mice (F.J. Giordano et al., *PNAS 98*(10):5780-5785 (May 8, 2001)). Attached hereto as Attachment E is a copy of a publication that discloses that introduction of a gene encoding vascular endothelial growth factor into the limbs of human patients suffering from leg ischemia (blocked blood vessels) improved blood flow in the limbs, and relieved other symptoms of the ischemia (K.-G. Shyu et al., *The American Journal of Medicine 114*:85-92 (February 1, 2003)). Attached hereto as Attachment F is a copy of a publication that reviews progress in gene therapy using vascular endothelial growth factor (Baumgartner, I., *The American Journal of Medicine 114*:156-157 (February 1, 2003)). This publication discloses, *inter alia*, the successful use of vascular endothelial growth factor gene therapy to promote blood vessel formation. Applicants submit that, taken together, the foregoing publications (Attachments D-F) demonstrate that mouse is a useful model system for studying blood vessel

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formation (such as the blood vessel formation that occurs during a wound response), and that results observed in mice can be extrapolated to human beings.

Thus, applicants submit that, in the area of wound healing and blood vessel formation, experimental results observed in mice are predictive of the same response in humans. In particular, applicants submit that the results reported in Example 1 of the present application can be extrapolated to human beings with reasonable certainty.

The Examiner further argues that the specification provides no particular guidance or direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question. Contrary to the Examiner's assertion, page 19, lines 12-14, of the present application set forth that representative methods of delivery for, *inter alia,* antisense TSP2 molecules, include any of the methods of delivering nucleic acid molecules into living cells described in the present patent application. The aforementioned methods for delivering nucleic acid molecules into living cells are set forth at page 13, line 3 through page 15 of the present application.

The Examiner further asserts that Kyriakides et al. (*Journal of Controlled Release 78*:295-303, 2002) disclose that the efficacy of antisense treatments to decrease thrombospondin 2 expression is difficult to assess, and specifically addresses the unpredictability associated with the antisense therapeutic art with regard to thrombospondin 2. The portion of the Kyriakides et al. publication relied upon by the Examiner occurs at page 302 in the second paragraph of the first column, and is reproduced here:

> The efficacy of antisense treatments to decrease TSP2 expression was difficult to assess. In day 14 WT wounds, control DOTAP-DNA formulations exhibited TSP2 deposition that was predominantly cell-associated and with variable levels, similar to that reported for wild wounds [8]. The variability of TSP2 expression

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along with the presence of inflammatory cells that do not express TSP2 prevented us from accurately determining the extent of reduction in TSP2 expression. However, we were able to observe biological changes induced by both the antisense and sense TSP2 treatments. (Underline added.)

Although Kyriakides et al. met some difficulties in assessing the efficacy of antisense treatments to decreased TSP2 expression, Kyriakides et al. nonetheless clearly state that the antisense treatments decreased TSP2 expression. Thus, the Kyriakides et al. publication cited by the Examiner shows that antisense TSP2 nucleic acid molecules improve the wound response in mice.

With respect to the Crooke (*Basic Principles of Antisense Therapeutics*, Springer-Verlag, NY, pages 1-50), Branch (*TIBS 23*:45-50, February 1998) and Jen et al. (*Stem Cells 18*:307-319, 2000) publications cited by the Examiner to support the contention that the antisense art is unpredictable in general, applicants respectfully point out the claimed invention is not directed to the antisense art in general, but to the use of specific types of antisense nucleic acid molecule to modulate the wound response. Irrespective of whether other types of antisense molecules may be unpredictable, applicants have shown, in mice, that antisense TSP2 nucleic acid molecules are capable of modulating the wound response and that there is a reasonable basis for expecting that these results are reproducible in humans.

Moreover, it appears that the Examiner has selected the Crooke, Branch and Jen et al. publications, from all of the available literature relating to antisense technology, to attempt to characterize antisense technology as very unpredictable and almost certain to fail. Applicants respectfully submit that the Examiner has mischaracterized the state of antisense technology by selecting only those publications that support the Examiner's position. Applicants submit that it is well within the ability of one of ordinary skill in the art to make and use effective antisense

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nucleic acid molecules. Examples of the successful use of antisense nucleic acid molecules are provided by two of the publications cited by the Examiner in Paper Number 9: Gardner et al. (*Oncogene 9*:2321-2326, 1994) discloses the successful use of antisense mRNA molecules to reduce osteopontin synthesis in transformed rat fibroblasts *in vitro*; and Okada et al. (*American Journal of Physiological and Renal Physiology 278*:F110-F121, 2000) discloses the successful use of antisense osteopontin oligodeoxynucleotides, *in vivo*, to reduce renal osteopontin synthesis in rat.

Thus, applicants respectfully submit that the claimed invention is fully enabled by the specification.

Rejection of Claims 1-7 and 10-18 Under 35 U.S.C. § 112, First Paragraph, for Alleged Lack of Enablement With Respect to the use of Osteopontin

The Examiner argues that the specification does not provide particular guidance or particular direction for a method for modulating the amount or biological activity of osteopontin using a molecule consisting of osteopontin, wherein the molecule consisting of osteopontin improves the wound response in a human being. The Examiner acknowledges that Example 2 of the instant application discloses that osteopontin null mice demonstrate high levels of foreign body giant cells surrounding an implant. The Examiner acknowledges that Example 3 of the instant application discloses that osteopontin immobilized in the surface layer of an implanted device causes a reduction of both fibrous capsule thickness and macrophage infiltration surrounding the implanted device.

Applicants submit that Example 3 therefore discloses at least one method for effectively delivering osteopontin molecules to a mammalian subject; by incorporating the osteopontin molecules into the surface layer of an implanted medical device, thereby reducing both fibrous

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capsule thickness and macrophage infiltration surrounding the implanted device, and so extending the useful life of the implanted device.

The Examiner argues that the specification provides no particular nexus between the reduction in fibrous capsule thickness and macrophage infiltration surrounding an implanted device to modulating the amount, or biological activity, of osteopontin to improve the wound response in humans. Contrary to the Examiner's assertion, and for the reasons set forth in the preceding section, directed to the rejection of Claims 1-7 and 10-18 for alleged lack of enablement with respect to the use of thrombospondin 2, applicants submit that mouse is an art-recognized model for studying the mammalian wound response, and that results obtained in mice with respect to the wound response can be extrapolated to human beings. Thus, applicants submit that the observation in mouse that the provision of osteopontin at the site of a wound reduces the foreign body reaction can be extrapolated to human beings with reasonable certainty.

The Examiner further argues that the specification provides no particular guidance or direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question. Contrary to the Examiner's assertion, representative methods for delivering nucleic acid molecules, that encode and express osteopontin, into living cells are set forth at page 13, line 3 through page 15 of the present application. Additionally, pages 16 and 17 of the present application set forth representative methods for delivering osteopontin protein to a living subject.

The Examiner relies on the publications by Crooke (*Basic Principles of Antisense Therapeutics*, Springer-Verlag, NY, pages 1-50), Branch (*TIBS 23*: 45-50, February 1998) and Jen et al. (*Stem Cells 18*:307-319, 2000) to support the assertion that *in vivo* nucleic acid delivery and therapy is unpredictable. Applicants respectfully point out that each of the foregoing publications only deals with the use of antisense nucleic acid molecules. None of these

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publications more generally discusses "the level of predictability or unpredictability associated with *in vivo* nucleic acid delivery and therapy" as asserted by the Examiner. Thus, for example, the Crooke, Branch and Jen et al. publications do not discuss the expression of nucleic acid molecules encoding a therapeutic protein (*e.g.*, osteopontin) in order to increase the amount of the protein within a mammalian body.

The Examiner relies on the O'Regan et al. publication (*International Journal of Experimental Pathology 81*:373-390, 2000) for the assertion that the precise role of osteopontin *in vivo* remains unclear. It appears that the Examiner is arguing that the use of osteopontin to modulate the wound response is unpredictable because all of the functions of osteopontin, *in vivo*, are not fully understood. Applicants respectfully submit that they are not required to fully understand all of the functions of osteopontin in a living subject. The issue is whether osteopontin functions in the claimed method, and whether applicants have taught one of ordinary skill in the art how to practice the claimed method. In Example 3 of the present application, applicants have provided data showing that osteopontin modulates the wound response in mice *in vivo*. For the reasons set forth herein, applicants submit that these data are predictive of the effect of osteopontin in human beings, and that the present application provides sufficient information to teach one of ordinary skill in the art how to use osteopontin to modulate the wound response in an animal.

Rejection of Claims 1 and 11 under 35 U.S.C. § 102(b) as Being Allegedly Anticipated by Liaw et al. (*Journal of Clinical Investigation 101*:1468-1478, 1998)

In relevant part, Claim 1, from which Claim 11 depends, is directed to a method of modulating the amount or biological activity of osteopontin in an animal, the method comprising the step of introducing into the animal an amount of osteopontin effective to modulate the amount or biological activity of osteopontin in the animal.

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It is applicants' understanding that the Liaw et al. reference teaches the use of an osteopontin replacement vector in which exons 4-7 of osteopontin are replaced by a marker, thereby inactivating the osteopontin gene. Thus, the Liaw et al. publication does not teach the introduction of osteopontin into an animal. Indeed, the Liaw et al. publication teaches the inactivation of the osteopontin gene. Consequently, the Liaw et al. does not anticipate Claims 1 and 11.

Rejection of Claims 1 and 11 Under 35 U.S.C. § 102(b) as Being Allegedly Anticipated by Gardner et al. (*Oncogene 9*:2321-2326, 1994)

The Examiner characterizes Gardner et al. as disclosing the reduction in osteopontin synthesis by antisense RNA expression in transformed fibroblast cells. Again, applicants note that, in relevant part, Claims 1 and 11 require the introduction of osteopontin into an animal in order to modulate the amount or biological activity of osteopontin in the animal. The Gardner et al. publication does not disclose the introduction of osteopontin into an animal, and so does not anticipate Claims 1 and 11 as asserted by the Examiner.

Rejection of Claims 1 and 11 Under 35 U.S.C. § 102(a) as Being Allegedly Anticipated by Okada et al. (*American Journal of Physiological and Renal Physiology 278*:F110-F121, 2000)

The Examiner characterizes Okada et al. as disclosing the reduction in osteopontin synthesis by antisense RNA molecules. Again, applicants note that, in relevant part, Claims 1 and 11 require the introduction of osteopontin into an animal in order to modulate the amount or biological activity of osteopontin in the animal. The Okada et al. publication does not disclose the introduction of osteopontin into an animal, and so does not anticipate Claims 1 and 11 as asserted by the Examiner.

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Rejection of Claims 1-7 and 10 Under 35 U.S.C. § 102(e) as Being Allegedly Anticipated by Streit et al. (U.S. Published Patent Application No. 2002/0119921)

The Examiner characterizes the Streit et al. patent application as disclosing a method of modulating thrombospondin 2 (TSP2) activity by administering a TSP2 antisense or TSP2 ribozyme that binds to cellular TSP2 mRNA and inhibits expression of the protein. Applicants note that the Streit et al. patent application was filed on March 30, 2001, and claims benefit of priority from U.S. Application No. 09/536,087, filed on March 24, 2000, and from U.S. Provisional Application No. 60/127,221, filed on March 31, 1999. In the context of the Examiner's rejection of Claims 1-7 and 10, the effective date of the Streit et al. patent as a reference under 35 U.S.C. § 102(e) is the filing date of the earliest filed of the foregoing applications which discloses a method of modulating thrombospondin 2 activity by administering a thrombospondin 2 antisense or thrombospondin 2 ribozyme that binds to cellular thrombospondin 2 mRNA and inhibits expression of the protein.

The present application claims the benefit of priority of United States Provisional Patent Application No. 60/222,071 which was filed on August 1, 2000. A copy of United States Provisional Patent Application No. 60/222,071 (hereinafter referred to as the '071 application) is attached hereto as Attachment G. The '071 application discloses, *inter alia*, the implantation of a collagen matrix into mice. The collagen matrix was impregnated with antisense TSP2 molecules. The antisense TSP2 molecules promoted vascularization of the fibrous capsule that formed around the implanted matrix (*see, e.g.*, FIGURE 3, and discussion thereof). Thus, the '071 application discloses the claimed use of TSP2 antisense molecules to modulate the amount or biological activity of TSP2 in an animal. Thus, the priority date of this aspect of the invention is August 1, 2000.

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If the portion of the Streit et al. published patent application that discloses a method of modulating thrombospondin 2 activity, by administering a thrombospondin 2 antisense or thrombospondin 2 ribozyme that binds to cellular thrombospondin 2 mRNA and inhibits expression of the protein, is later than August 1, 2000, then that portion of the Streit et al. published patent application is not prior art with respect to the present application. Applicants have made a *bona fide* attempt to obtain the prosecution history of the Streit et al. published patent application from the United States Patent and Trademark Office. To date, however, applicants have been unable to obtain this prosecution history because the file is located in an Art Unit and is not immediately available for copying. Applicants continue to try to obtain a copy of the prosecution history of the Streit et al. patent application in order to definitively address the availability of the Streit et al. published patent application as prior art with respect to Claims 1-7 and 10 of the present application. In the meantime, applicants question whether the Streit et al. patent application is prior art with respect to any portion of the present application.

CONCLUSIONS

In view of the foregoing claim amendments and arguments, applicants submit that all of the pending claims are in condition for allowance. Reconsideration and favorable action are requested.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: July 23, 2003 Pamela M Jenkins

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